REMARKS

Upon entry of this response, claims 13-19 and 26-28 will remain pending, with claims 13, 15 and 17-19 being independent claims.

Reconsideration and allowance of the application are respectfully requested.

Response To Rejection

The following rejection is set forth in the Office Action:

Claims 13-19 and 26-28 are rejected under 35 U.S.C. 102(b) as being anticipated by Engman et al. (hereinafter "Engman"), "Diaryl Chalcogenides as Selective Inhibitors of Thioredoxin Reductase and Potential Antitumor Agents", Anticancer Research, Helenic Anticancer Institute, Anthens, GR, Vol. 17, No. 6D, 1997, pp. 4599-4605.

Applicants submit that the rejection is without appropriate basis in that (as previously argued by Applicants throughout the lengthy prosecution of this application) Engman discloses that ebselen was found to be an inhibitor of human thioredoxin reductase. Engman does not disclose the use of ebselen as a substrate for thioredoxin reductase. See, for example, the abstract of Engman.

As Engman was looking at ebselen as an inhibitor, Engman used conditions wherein ebselen is used as an inhibitor and not as a substrate. Accordingly, Engman does not disclose each and every feature of Applicants' claims including the conditions recited in Applicants' claims. In particular, Engman discloses in his assay, at page 4600, the paragraph bridging the right and left-hand columns, that, "Thioredoxin reductase activity was measured spectrophotometrically at room temperature by the oxidation of NADPH at 339 nm in the presence of 15μM human recombinant thioredoxin **and 1 mg/ml bovine insulin**." (Emphasis added.)

Thus, in each of the assays of Engman, insulin is present. Insulin in the assay affects the results, and is included in the assay apparently because Engman was experimenting with ebselen as an inhibitor. The conditions used by Engman are not conditions as recited in Applicants' claims that achieve the results recited in Applicants' claims.

Therefore, Engman does not teach each and every feature recited in Applicants' claims. Engman does not constitute anticipatory prior art as asserted in the rejection, because:

(1) Engman does not disclose, as recited in Applicants' independent claim 13, a method for reduction of a substrate with thioredoxin reductase, comprising combining the thioredoxin reductase, the substrate and NADPH *in vitro* under conditions to reduce the substrate, the substrate being as recited in Applicants' claim 13.

(2) Engman does not disclose, as recited in Applicants' independent claim 15, a method of enhancing peroxidase activity of thioredoxin reductase, comprising combining NAPDH, thioredoxin reductase, thioredoxin and a substrate *in vitro* under conditions to enhance peroxidase activity of thioredoxin reductase, the substrate being as recited in Applicants' claim 15.

(3) Engman does not disclose, as recited in Applicants' independent claim 17, a method of oxidizing reduced thioredoxin by a substrate, the method comprising combining reduced thioredoxin and a substrate *in vitro* under conditions to oxidize the reduced thioredoxin with the substrate, the substrate being as recited in Applicants' claim 17.

(4) Engman does not disclose, as recited in Applicants' independent claim 18, a method for reducing a peroxide comprising combining thioredoxin, thioredoxin reductase, NAPDH and a substrate *in vitro* under conditions to reduce the peroxide, the substrate being as recited in Applicants' claim 18.

(5) Engman does not disclose, as recited in Applicants' independent claim 19, a method of preventing peroxidation of a substance comprising combining thioredoxin, thioredoxin reductase and NADPH with a substrate *in vitro* under conditions to prevent peroxidation of the substance , the substrate being as recited in Applicants' claim 19.

The Examiner is reminded that in contrast to the prior art of record, the present invention recognizes and demonstrates that ebselen is a substrate being reduced by NADPH and thioredoxin reductase with a low Km-value meaning that it is a very good substrate undergoing unlimited cycles of oxidation/reduction in the presence of hydrogen peroxide without affecting the activity of the enzyme. The reduced ebselen is called ebselen selenol and has the Se-N bond broken by reduction. The selenol is oxidized back to ebselen by hydrogen peroxide or another peroxide and a new cycle starts. The reaction is ultimately driven by NADPH. Reduced thioredoxin strongly enhances the thioredoxin reductase reaction which is also proven by determination of the rate of reduction of ebselen by reduced thioredoxin using kinetics with tryptophan fluorescence. The result, never seen before, is that ebselen is a very efficient oxidant of reduced thioredoxin.

Accordingly, for at least the reasons set forth above, each of the pending claims is patentable over Engman, and the rejection should be withdrawn.

CONCLUSION

In view of the foregoing, the Examiner is respectfully requested to reconsider and withdraw the rejection of record, and allow each of the pending claims.

Applicants therefore respectfully request that an early indication of allowance of the application be indicated by the mailing of the Notices of Allowance and Allowability.

Should the Examiner have any questions regarding this application, the Examiner is invited to contact the undersigned at the below-listed telephone number.

Respectfully submitted,
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